1: J Hematother. 1992 Spring;1(1):85-94. Related Articles, Links

Initial trial of bispecific antibody-mediated immunotherapy of CD15-bearing tumors: cytotoxicity of human tumor cells using a bispecific antibody comprised of anti-CD15 (MoAb PM81) and anti-CD64/Fc gamma RI (MoAb 32).

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The high-affinity receptor for IgG, Fc gamma RI, expressed on monocytes and interferon-gamma (IFN-gamma)-stimulated neutrophils, is a trigger molecule for cell-mediated cytotoxicity. We have prepared murine monoclonal antibodies (MoAb 22 and MoAb 32) that bind to Fc gamma RI outside the ligand binding site and thus bind to and trigger cytotoxicity that is not competed by other immunoglobulins. Because of these properties, it seemed that these MoAbs would be very useful for the development of bispecific antibodies (BsAb) for targeting normal cellular immune defense mechanisms as a new form of immunotherapy for treatment of cancer. BsAbs incorporate into a single molecule the binding specifities of two different antibodies, and, thus, can be used to target myeloid cells to tumors, ensure activation of cellular cytotoxic mechanisms, and target cell lysis and/or phagocytosis. BsAbs were prepared using anti-Fc gamma RI MoAb and an anti-myeloid cell MoAb, PM81, reactive with the CD15 antigen, for studies of antibody-dependent cellular cytotoxicity. Conjugates were made by cross-linking sulfhydryl groups of Fab fragments of MoAb 32 or 22 (both IgG1) and sulfhydryl groups added to intact PM81 (an IgM) using N-succinimdyl-acetyl-S-thioacetate (SATA). The resulting product was purified by high-performance size-exclusion chromatography. The ability of the BsAbs to mediate attachment of human monocytes to tumor target cells was confirmed in a microtiter well assay of binding of MTT-labeled U937 cells (a human Fc gamma RI-bearing cell line) to SKBR-3 (PM81-reactive breast carcinoma) target cells. The ability of the BsAbs to mediate killing of HL-60 promyelocytic leukemia cells was studied using a 6-hour Chromium-51 release assay. Effector cells were monocytes obtained by cytopheresis and cultured for 18 hours with IFN-gamma. Monocytes alone caused minimal killing (5-20%), monocytes plus BsAb caused moderate killing (20-50%), and monocytes plus BsAb plus human serum resulted in maximal killing (50-80%). Experiments were performed to test the ability of the BsAb to purge bone marrow of small numbers of leukemia cells using bone marrow mononuclear phagocytes treated for 18 hours with IFN-gamma prior to adding target cells. Without the addition of human serum as a source of complement, a 90% depletion of clonogenic HL-60 cells could be demonstrated. With human complement, up to 95% depletion was seen. Thus, this BsAb possessed the ability to lyse tumor cell targets by two different mechanisms, complement and cell-mediated lysis.

(ABSTRACT TRUNCATED AT 400 WORDS)

Publication Types:

- Clinical Trial
- Clinical Trial, Phase I

PMID: 1365020 [PubMed - indexed for MEDLINE]
